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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/546,201	04/10/2000	John M. Polo	930049.464/1463.002	3605

7590 01/25/2005

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/546,201	POLO ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-31 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-31 and 33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26, 28-31 and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubensky, Jr. et al. (US 6,015,686), which is hereinafter referred to as "Dubensky", Cella et al. (Journal of Experimental Medicine. March 1, 1999; 189 (5): 821-829), hereinafter "Cella", Chada et al. (US 5,736,388), hereinafter "Chada" and Gillespie et al. (WO 90/14090), hereinafter "Gillespie" for reasons of record.

Applicant reiterates that none of the references teach all of the claimed elements individually and that no combination of the references result in teaching the instant invention.

Applicant's statement has been fully considered, but is found unpersuasive because all of the required elements in the claims are taught by the combination of references (emphasis added). While applicant repeats that no one reference teaches all of the claimed limitations, applicant has not pointed to a single limitation that is missing from the combination of references. It is conceded that no one reference teaches all of the claimed limitations, i.e. that no single reference anticipates the invention. However, the combination of references cited teaches all of required elements of the claims.

The following summarizes all of the required limitations of the instant claims as well as the page and line number within each of the references that the required limitations are taught.

(Although motivations for combining the limitations with a reasonable expectation of success are also taught by the references, this discussion is presented later.) The instant claims require:

An expression cassette comprising:

1) a promoter operably linked to a nucleic acid molecule, which when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences, that induces the production of interferon and

2) RNA polymerase II operably linked to a nucleic acid encoding an antigen from a pathogenic agent.

Claims 28 and 29 state that the antigen is a viral antigen selected from HIV, HSV, HBV, HCV, HPV and FIV. Claim 30 states that the pathogenic agent is a bacteria, a parasite or a fungus and claim 31 states that the pathogenic agent is a tumor. Claim 33 requires that the pol II promoter is selected from CMV, SV40, MoMLV LTR and RSV LTR. Claim 34 is drawn to a gene delivery vector comprising the instant expression cassette. Claim 44 is drawn to a cell containing the gene delivery vector of claim 34. Claims 35-43 state that the vector is a plasmid, a recombinant retrovirus, a recombinant herpesvirus, a recombinant poxvirus, a recombinant adenovirus, a recombinant parvovirus, a recombinant alphavirus, a recombinant polyomavirus, and a eukaryotic layered vector initiation system, respectively.

The combined prior art teaches the following required elements:

Dubensky teaches a eukaryotic layered vector initiation system comprising a promoter that expresses a heterologous sequence, see claims 1 and 2. The heterologous sequence is

derived from a virus and is selected from HIV, HBV, HCV, FIV, see claim 9, as well as HSV and HPV, see column 4, lines 36-39. Dubensky also teaches that the vector construct can encode proteins from bacteria, parasites or fungus, see column 23, lines 30-36. Additionally, the vector of Dubensky encodes a cancer gene, see column 27, line 60 to column 28, line 2.

The promoter that initiates the synthesis of viral RNA encoding the heterologous gene of Dubensky is selected from the group consisting of the following: CMV, SV40, MoMLV LTR and RSV LTR, see claim 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56, column 101, lines 42-57. These promoters are identical to the promoters listed in instant claim 33.

Dubensky teaches that a wide variety of vectors may be utilized in the eukaryotic layered vector initiation system, such as retroviruses, herpesviruses, poxviruses, adenoviruses, parvoviruses, alphaviruses and polyoma viruses, see column 32, lines 26-67. Dubensky also teaches that the expression vector is a plasmid, see column 36, line 44 to column 37, line 16 and column 56, line 47 to column 57, line 11 for example. Dubensky teaches a cell containing the gene delivery vector in claim 12.

Dubensky also teaches that antisense RNA forming large quantities of double-stranded RNA is utilized in the expression system. The double-stranded RNA increases the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13. Dubensky also claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompass an antisense RNA that forms double-stranded RNA. Therefore, Dubensky teaches a construct encoding a polymerase II promoter encoding an antigen from a pathogenic

agent, as well as a construct encoding a nucleic acid that forms double-stranded RNA for the induction of interferon, see the previous citations.

Dubensky does not teach dsRNA with self-complementing sequences.

However, Gillespie teaches dsRNA with complementing sequences from a vector construct to induce the production of interferon. See page 4, line 10 to page 6, line 18, Figures 1-4 and claims 1-16.

Dubensky does not teach a single construct comprising a first promoter expressing a heterologous antigen and another promoter encoding a nucleic acid that forms double-stranded RNA. However, Dubensky explicitly teaches that the expression vector is used to express multiple heterologous genes, see column 16, line 61 to column 17, line 29 and column 85, line 50 to column 94, line 18. In addition, Chada also teaches a eukaryotic layered vector initiation system that utilizes the same viral vectors and the same promoters of Dubensky, see column 16, line 48 to column 17, line 21. Chada et al. states that one promoter within the same construct may be inadequate to ensure an adequate level of expression of all heterologous genes, see column 26, lines 4-21, thereby providing explicit motivation to express multiple heterologous genes of Dubensky from different promoters within the same construct.

Applicant argues that Gillespie does not provide motivation to combine teachings with Dubensky, Cella and Chada. More specifically, applicant argues that Dubensky, Cella, Chada and Gillespie do not teach or suggest self-complementing dsRNA *in vivo*. Applicant asserts that motivation for combining different teachings must be found in the references themselves.

However, obviousness is either established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves, as applicant states, or in the knowledge generally available to one of ordinary skill in the art (emphasis added). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, motivations for combining the teachings have always been found directly within the teachings of the references.

Gillespie is cited to teach self-complementary dsRNA, which is not taught by the other references. Gillespie explicitly discusses transcription of a plasmid expressing self-complementing dsRNA from a promoter, see page 5, lines 3-8, 25-29, page 6, lines 5-6 and Figure 3. Gillespie also specifically teaches evaluation of antitumor properties with dsRNA *in vitro* and *in vivo*, see page 7, lines 16-22. Dubensky claims a method of delivering a heterologous nucleic acid to an animal by administering the eukaryotic layered vector initiation system, see claim 18. The heterologous nucleic acid expressed within the eukaryotic layered vector initiation system of Dubensky is an antisense sequence, a non-coding sense sequence or a riboyme sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompasses an antisense RNA that forms double-stranded RNA, see column 23, lines 1-13. Therefore, contrary to applicant's assertions, Dubensky explicitly claims *in vivo* expression of dsRNA from an expression vector. Not only do the references teach the instant elements claimed, but the references also teach explicit motivation for expressing dsRNA from the vector system of Dubensky. The motivation for expressing the dsRNA in each of the references is as follows: Dubensky teaches that double-stranded RNA increases the expression of

gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13, Gillespie also teaches inducing the production of interferon by administering dsRNA, see claims 9-16 and Cella teach that double-stranded RNA induces interferon, protects against cytopathic effects of a virus in dendritic cells and increases the capacity of dendritic cells to prime T cells, see the abstract and the first two paragraphs in the discussion section on page 826. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to induce the production of interferon with the complementary, double-stranded RNA of Gillespie to protect dendritic cells from viral infection and generate a CTL response to a viral infection, see page 821 and the first two paragraphs in the discussion section on page 826 of Cella and elicit a specific immune response with a viral antigen of Dubensky and induce the production of interferon, taught by Dubensky and Gillespie.

Applicant concludes that Gillespie teaches that expression vectors are unnecessary for making dsRNA, that Gillespie prefers treatment of the dsRNA with RNase A prior to use and only induces interferon with dsRNA formed *in vitro*.

A review of the reference has been fully considered, but is found unpersuasive. Gillespie explicitly teaches expression of complementary dsRNA from plasmid DNA, see page 5, lines 3-8, 25-29, page 6, lines 5-6 and Figure 3 for example. Therefore, transcription of dsRNA from a vector is explicitly taught. Regarding treatment with RNase A, the citation quoted by applicant states, "This hinged dsRNA can be used as is or can be trimmed with RNase...(emphasis added)". The "or" clearly does not indicate preferential treatment, but merely an alternative. The sole expression of inducing interferon with dsRNA formed *in vitro* asserted by applicant is not conclusive since the dsRNA of Gillespie is transcribed in cells from a plasmid vector, see

page 5, lines 3-8, 25-29, page 6, lines 5-6 and Figure 3, and the cells could be in tissue culture or in animals, see page 7, lines 16-22. In any case, *in vivo* expression of dsRNA from a vector is claimed by Dubensky, see claims 1, 10 and 18.

Applicant further argues that the combination of references do not provide a reasonable expectation of success for producing self-complementing dsRNA *in vivo* or induce the production of interferon upon transcription with dsRNA or that the expression cassettes could include additional coding sequences.

Applicant's arguments have been fully considered, but are found unpersuasive. Regarding self-complementation of dsRNA *in vivo*, Gillespie explicitly teaches the transcription of self-complementary dsRNA from a plasmid vector within a cell, see page 5, lines 3-8, 25-29, page 6, lines 5-6 and Figure 3 as well as page 7, lines 16-22. Further, *in vivo* expression of dsRNA from a vector cassette is encompassed by Dubensky, see claims 1, 10 and 18. Contrary to applicant's assertion, these explicit teachings provide more than a reasonable expectation of success for producing self-complementing dsRNA *in vivo*. Regarding the production of interferon, this appears to be the primary function of dsRNA according to the prior art, see column 23, lines 1-10 of Dubensky, claims 9-16 of Gillespie and the abstract and the first two paragraphs in the discussion section on page 826 of Cella. Regarding the multiple expression of heterologous sequences, Dubensky explicitly teaches an expression vector comprising a promoter that is used to express multiple heterologous genes, see column 16, line 61 to column 17, line 29, column 85, line 50 to column 94, line 18, claims 1, 2, 9, 10, column 4, lines 36-39, column 23, lines 30-36 and column 27, line 60 to column 28, line 2. In addition, Chada provide explicit motivation for expressing different heterologous sequences from different promoters to

ensure an adequate level of expression of all heterologous genes, see column 26, lines 4-21. Further, the ordinary artisan would have had more than a reasonable expectation of success for expressing multiple heterologous sequences from different promoters in the expression cassette of Dubensky because the vector of Chada is also a eukaryotic layered vector initiation system.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 10:00 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shanon Foley
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Art Unit 1648